British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1358

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

*Proceedings of the 14th APS International PharmSci 2023*

# Developing a Robust In Vitro Release Method for a Polymeric Nanoparticle: Challenges and Learnings

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ARTICLE INFO

Received: 06/06/2023
Accepted: 08/07/2023
Published: 30/12/2023

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KEYWORDS: Polymeric nanoparticles; In vitro release; Dispersion Releaser; NanoDis

SUMMARY

Nanomedicines have been highlighted as a promising approach for targeted drug delivery, as they can improve drug efficacy and reduce systemic toxicity. Due to the wide range of formulation types and the complex nature of the drug release mechanism, the development of an in vitro release (IVR) method for nanomedicines is challenging and regulatory guidance is limited. In this work, we are outlining the IVR method development for a controlled-release polymeric nanoparticle. This included the optimisation of the release medium composition and the selection of an appropriate sampling technique for the isolation of the released drug from the formulation. In addition to the established ultracentrifugation, the NanoDis showed potential as an automated technique.



## INTRODUCTION

Nanomedicines are a promising candidate for targeted drug delivery, particularly in cancer therapies. AZD2811, an inhibitor of Aurora B kinase, has demonstrated efficacy when tested for various tumours in clinical trials, but also toxicity. To overcome the toxic side effects, the drug was formulated in controlled-release polymeric nanoparticles using the Accurins™ technology together with pamoic acid as a counterion to improve encapsulation efficiency and decrease the release rate (Ashton, Song et al. 2016). The unique nature of nanomedicines renders the development of an IVR method for nanomedicines challenging. This work presents the extensive IVR method development for AZD2811 nanoparticles through the optimisation of the release medium composition and sampling technique.

## MATERIALS AND METHODS

Most chemicals were purchased from Sigma-Aldrich. NanoDis filters and Dispersion Releaser membranes were purchased from Repligen.

**AZD2811 IVR method:** The nanoparticle suspension was thawed and a sample was added to 50 mL of release medium in glass jars at a concentration of 0.02 mg/mL and incubated in a shaking waterbath at 75 rpm. The original release medium, 10 mM Phosphate Buffered Saline (PBS) pH 7.4, was optimised to 100 mM Sorensen's phosphate buffer pH 6.9 with 150 mM NaCl and 0.06 mg/mL BHA. Samples were taken at selected timepoints with one of the following techniques and analysed with UHPLC:

**Ultracentrifugation**: 3.2 mL samples were ultra-centrifuged at 110,000 rpm and 4°C for 30 minutes.

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0.25 mL of supernatant and 0.25 mL of release medium were analysed to give the released and total API concentration, respectively.

**NanoDis**: Sampling cannulas were placed in the glass jars and MicroKros mPES, MWCO 300 kDa, 20 cm x 0.5 mm, Cross Flow Filters (CFF) were used to isolate the released API from the formulation.

**Dispersion Releaser:** The Dispersion Releaser is a modified USP2 apparatus, with a sample dialysis cell in the place of the paddles. 0.5 mL samples were taken from the release medium for analysis.

**UHPLC analysis:** The concentration of AZD2811 was measured using ultra-high performance liquid chromatography coupled with an ultraviolet detector (UHPLC-UV) at 258 nm and mobile phases A (0.1% v/v TFA in water) and B (0.08% v/v in acetonitrile). A C18 reverse phase column (Waters CSH C18) was used with a flow rate of 0.3 mL/minute and a mobile phase gradient of mobile phase B from 15% to 20% over 4 minutes and then 20% to 85% over 2 minutes.

## RESULTS AND DISCUSSION

The lack of robustness of the original IVR method was associated with the degradation of the API and the surfactant, as well as the drift of the pH of the release medium during the test. 10 mM PBS pH 7.4 was replaced by a 100 mM Sorensen's phosphate buffer pH 6.9 which maintained the pH for the duration of the test and butylated hydroxy anisole was added to the medium to minimise degradation via the formation of N-oxides.

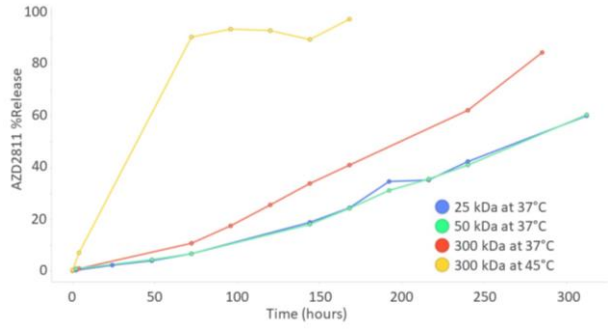


***Fig. 1.*** *AZD2811 IVR release profiles generated with the Dispersion Releaser with a range of MWCO membranes.*

Although ultracentrifugation has been validated as a separation technique, it is time consuming and labour intensive. Assessment of the Dispersion Releaser revealed that membrane kinetics were interfering with the accurate measurement of drug release from the nanoparticles, resulting in a lag phase (Figure 1). On the other hand, the NanoDis proved to be compatible with the AZD2811 nanoparticles and generated accurate and detailed release profiles (Figure 2).

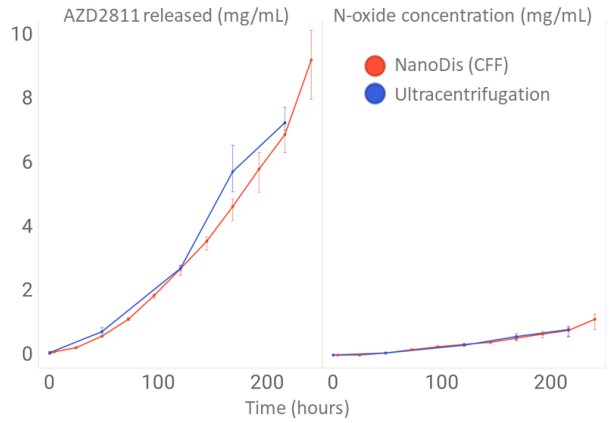


***Fig. 2.*** *AZD2811 IVR release profiles and low N-oxide concentrations measured with the NanoDis*

## CONCLUSIONS

A robust IVR method for AZD2811 polymeric nanoparticles was developed. The optimisation of the release medium composition was critical to provide method robustness and it was achieved by minimising drug and surfactant degradation, as well as maintaining the pH for the duration of the IVR test. The NanoDis showed great potential as an automated technique for the isolation of the released drug from the formulation.

## ACKNOWLEDGEMENTS

Agilent Technologies for the loan of the NanoDis system.

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